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# Transition path sampling on diffusive barriers

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## Abstract

We have adapted the transition path sampling algorithm for the study of activated diffusive processes in complex systems, in which the system has to overcome a high and rough free energy barrier. The new scheme is based on the stochastic shooting procedure and employs molecular dynamics trajectories with an Andersen thermostat as a noise generator. The algorithm is illustrated on a diffusive process in a dense Lennard-Jones fluid.

## 1. Introduction

Over the past few years, transition path sampling (TPS) has proved to be a viable method for studying activated processes in complex systems that cannot be investigated with straightforward molecular simulation techniques [1–7]. The major advantage of TPS is that one does not have to impose reaction coordinates on the system, but rather extracts these from the simulation results. Several complex processes have been studied so far and have been recently reviewed in [5].

The TPS method is based on the concept of the transition path ensemble, the collection of all possible dynamical pathways starting in a reactant state  $A$  and arriving in a product state  $B$  within a certain time [6]. The path ensemble can be sampled by an efficient Monte Carlo procedure called ‘shooting’. This procedure generates new trial paths in the ensemble from an existing trajectory by altering the system coordinates and/or momenta slightly at a random time along the trajectory, and integrating the equations of motion forward and backward in time. The trial path is accepted or rejected with a suitable acceptance criterion. The method works because the paths diverge quickly from the old trajectory due to the chaotic nature of the dynamics, and because the stable states  $A$  and  $B$  are attractors so the probability of obtaining a reactive path is still reasonable. Problems with the shooting version of TPS arise, however, if one wants to sample long deterministic trajectories over rough energy landscapes that cause the process to behave more diffusively. Diffusive transitions of this type are found in, for example, crystal nucleation or protein folding. The original shooting method is bound to fail for such barriers, because when the path is becoming too long, the old and the new trajectories will have diverged completely before the other basin of attraction is reached. In that case, a

small change in momenta will cause the forward as well as the backward trajectory to return to the same stable region. These nonreactive trajectories will make up the majority of the trial moves.

In this paper, we propose a new algorithm based on a stochastic TPS scheme, employing deterministic molecular dynamics (MD) trajectories with an Andersen thermostat as a noise generator [8] to increase the sampling efficiency. We will illustrate the application of this new algorithm on a simple model system.

Other methods have been developed to study diffusive barriers in complex systems. One of them is the stochastic path approach of Elber and co-workers [9, 10] and Eastman *et al* [11]. These methods are based on the Onsager–Machlup path action using very large time steps. This approach generates a path ensemble as a collection of trajectories, but these paths do not correspond to a microscopic dynamical rule [6]. Important information concerning e.g. solvent dynamics is lost in these methods, but is retained using the TPS techniques.

The paper is organized as follows. In section 2 we demonstrate the failure of the original shooting algorithm. This is followed by a description and illustration of the new TPS scheme in section 3. We end with concluding remarks.

## 2. Problems with diffusive barriers

### 2.1. Instability of long trajectories

As described in [4, 6] the TPS algorithm can be based on deterministic (Newtonian) trajectories as is done here, or, alternatively, stochastic Langevin or Monte Carlo trajectories. In the case of complex systems such as biomolecules undergoing conformational changes or crystal nucleation the use of deterministic trajectories as generated by MD has some advantages, such as the availability of efficient software packages. However, just *because* of the system's complexity, problems can arise with the instability of the dynamics. The TPS scheme relies on the reproducibility of trajectories, meaning that when the equations of motion are integrated forward and backward in time there should be a reasonable chance of obtaining a reactive pathway. If the acceptance ratio is (too) low, the momentum change  $dp$  can be made smaller until the probability for a reactive path is at an optimal value of 40% again [4]. For fast processes and short paths this procedure works very well [4, 6], because the new trajectory can be made to stay close to the old one. But the maximum path length is limited by the chaotic nature of the underlying dynamics, which can be quantified by the Lyapunov exponent  $\lambda$ . The distance  $\delta$  between phase space points on two trajectories that are initially very close will grow exponentially in time:  $\delta \propto \exp(\lambda t)$ . As for simple liquids, the Lyapunov exponents are of the order of  $\lambda \sim 1 \text{ ps}^{-1}$  [12]; a very small deviation from the initial condition, even on machine precision level (in double-precision arithmetic,  $\sim 10^{-15}$ ), already leads to considerable differences after a few picoseconds of simulation. For the backward integration in a shooting move the situation is even worse. Due to numerical round-off errors in the MD integrator, even a momentum displacement vector  $dp = 0$  will cause a reversed trajectory to diverge from the old one. The divergence of long trajectories reduces the chance of an accepted path, because a path that deviates from the old path before it reaches the other stable state will most likely return to the basin of attraction that it came from and thus fail to be reactive. Only if one is precisely at the transition state surface, defined by a 50% probability of reaching either stable state, is there a reasonable (25%) chance of obtaining a reactive trajectory [6]. In general, however, one is not at the transition surface and the acceptance probability will be much lower. Therefore, if the process of interest takes longer than a few picoseconds, molecular chaos will cause a trial trajectory almost certainly to fail to connect the initial and the final stable state.

## 2.2. Model system

We illustrate this effect on a model system in three dimensions consisting of  $N$  particles interacting via a Lennard-Jones pair potential truncated and shifted at the minimum, also called a WCA potential [13]:

$$V_{WCA}(r) = \begin{cases} 4\epsilon[(\sigma/r)^{12} - (\sigma/r)^6] + \epsilon & \text{if } r \leq r_c \equiv 2^{1/6}\sigma \\ 0 & \text{if } r > r_c, \end{cases} \quad (1)$$

where  $r$  is the interparticle distance, and  $\epsilon$  and  $\sigma$  specify the depth and the range of the potential, respectively. Throughout the paper we will use reduced units, i.e. energies in units of  $\epsilon$ , lengths in units of  $\sigma$ , masses in units of  $m$  and times in units of  $\tau \equiv (m\sigma^2/\epsilon)^{1/2}$ . In addition, two of the  $N$  particles interact with a double-well potential given by

$$V_{dw}(x) = \begin{cases} h(4(x - x_A)^2 - 1) & \text{if } x - x_A < 0.5\sigma \\ h(4(x_B - x)^2 - 1) & \text{if } x_B - x < 0.5\sigma \\ 0 & \text{otherwise.} \end{cases} \quad (2)$$

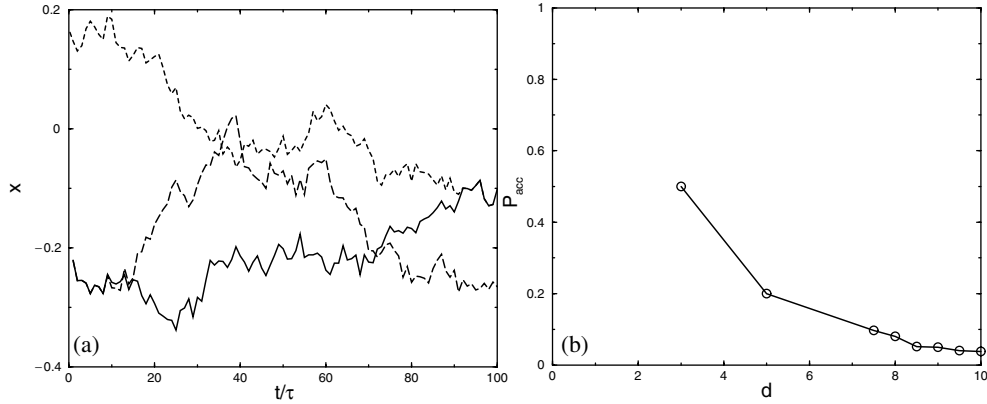
Here,  $x = x_2 - x_1$  is the distance along the  $x$ -axis between particles 1 and 2 and is always positive, i.e. particle 2 is always to the right of particle 1. The reason for using only the (positive)  $x$ -direction in the double-well potential instead of a general  $r$ -dependence is that it enables one to limit the number of particles. The periodic simulation box is therefore elongated in the  $x$ -direction and has dimensions  $13.68\sigma \times 5.13\sigma \times 5.13\sigma$ . This does not correspond to a physical situation but the system is only used for illustrative purposes anyway. In equation (2),  $x_A = 1.5\sigma$  is the position of the first minimum, and  $x_B = x_A + d$  is the position of the second minimum with  $d$  denoting the length of the flat barrier. Thus, the two particles can be in two states, either at a distance  $x_A$  or at a distance  $x_B$ . The harmonic potentials that keep the particles at these distances have a width of  $\sigma$  and a depth  $h$ . The above model describes a system which can jump from one stable state  $x_A$  to the other stable state at  $x_B$  by overcoming a high but rather flat, and hence diffusive, barrier. If  $h$  is large enough, the transitions between the two states become rare and the system will show exponential two-state behaviour.

The system evolves according to Hamilton's equation in a box with periodic boundaries. In all our simulations the number of particles was  $N = 288$ , the reduced density  $\rho = 0.8\sigma^{-3}$ , the time step  $\delta t = 0.01\tau$ , the total energy  $E = 446\epsilon$ , the depth of the harmonic potential  $h = 6\epsilon$ . On average the temperature was  $T = 0.68$ . This temperature and density correspond to a dense fluid. The equations of motion were integrated with the velocity Verlet algorithm with time step  $\delta t = 0.01\tau$ .

## 2.3. Numerical results

First, we investigated the numerical instability of the system. In figure 1(a) we plotted the  $x$ -position of a particle as a function of time. After  $100\tau$  the momenta were reversed and the path was integrated backward in time. At first, this reversed trajectory followed the old trajectory closely, but after  $10\tau$  it began to deviate due to numerical errors and became completely different. If one assumes that the model system is a reasonable approximation for liquid argon, this time corresponds to about 3 ps. Not only was reversing the momenta problematic, but also the forward integration suffered from instability. A change in momentum of a single particle by an amount  $10^{-15}$  led to a complete divergence after  $10\tau$ . This means that with a path length of a  $100\tau$  the acceptance probability will be determined by the energy landscape. If this landscape is rough and the process diffusive, the acceptance for shooting will be low.

Next, we performed a number of standard  $NVE$  path sampling simulations [6] on the system, with the stable state definitions  $A: x < x_1 + 0.4$  and  $B: x > x_2 - 0.4$ . The distance



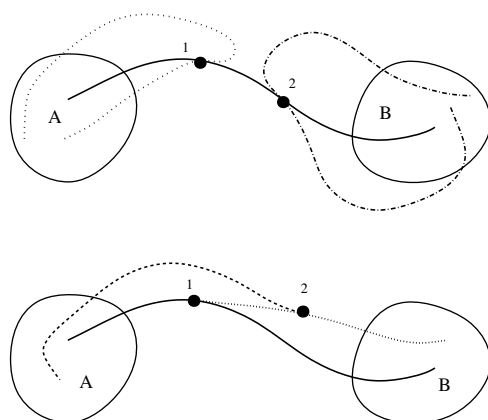
**Figure 1.** (a) Several trajectories visualized by the position  $x$  of one particle as a function of time. The solid curve is a trajectory for which all momenta are reversed after  $100\tau$  and the system is integrated backward in time (dashed curve). Initially, the reversed trajectory closely follows the original one (solid curve), but begins to diverge after about  $10\tau$ . The long-dashed curve is a trajectory that starts initially at the same phase space point as the solid curve, but with the  $z$ -momentum  $p_z$  of one random single particle changed by the absolute minimal amount  $10^{-15}$ . Integrating forward in time, this trajectory diverges as well after  $10\tau$ . (b) Acceptance ratio for the shooting move as a function of barrier width. In all cases the displacement vector was  $dp = 0.0001$ .

between the two stable states ranged from  $d = 3\sigma$  to  $11\sigma$ . The path length was  $\mathcal{T} = 100\tau$  and the total number of time slices on a path was set to  $L = 100$  for all simulations. For a shooting move, the displacement vector was chosen from a Gaussian distribution with a small width  $dp$ , and added to the old momentum, while conserving the total linear momentum and energy [4]. The shooting point time slice was randomly chosen between the last time slice in  $A$ ,  $t_A$ , and the first slice in  $B$ ,  $t_B$ . It was hence assumed that recrossing trajectories did not occur. Using these asymmetric generation probabilities, the acceptance rule becomes

$$P_{acc} = \min \left[ 1, \frac{t_B^{(o)} - t_A^{(o)}}{t_B^{(n)} - t_A^{(n)}} h_A(x_0^{(n)}) h_B(x_t^{(n)}) \right], \quad (3)$$

where the superscripts  $o$  and  $n$  refer to the old and the new paths, respectively. The characteristic functions for the stable regions,  $h_A(x_t)$  and  $h_B(x_t)$ , are equal to unity if  $x_t$  lies in  $A$  or  $B$  respectively, and vanish otherwise. In addition, besides each shooting move, on average ten shifting moves were attempted with the maximum shift of  $\mathcal{T}/2$ . To improve the statistics, 2000 short shifts of one time slice ( $=1\tau$ ) were also performed on average [4, 6].

In figure 1, the acceptance probability for shooting is plotted as a function of barrier width  $d$ . The acceptance probability decreases dramatically with the width, a general problem for diffusive barriers. The usual remedy for a low acceptance is to decrease the momentum change  $dp$ . However, as mentioned before this does not work for trajectories this long, where even the smallest possible value of  $dp$ , the machine precision, will cause the trajectories to diverge and will decrease the acceptance. For instance, in a TPS simulation for  $d = 10\sigma$  with  $dp = 0$  we found an acceptance ratio of 20% whereas it should be 100%. This ratio will quickly drop for larger barriers. In addition, if the total energy and the total linear momentum have to be conserved, it usually means that the momenta of all particles have to be rescaled to obey these constraints. Even for  $dp = 0$ , rescaling the velocities to a linear momentum of zero will introduce a change in momentum.



**Figure 2.** A schematic illustration of the failure of TPS to sample long trajectories on diffusive barriers. In the top figure the shooting move is performed on an initial trajectory (solid curve). Because of molecular chaos, the trial path (dotted curve) will diverge from the initial pathway, and will be attracted to *A* again. Therefore it is not reactive. Similarly, if the shooting is done on the other side of the transition state surface, the paths will be attracted to *B* instead, also leading to a nonreactive trajectory. The bottom figure shows what the one-way shooting scheme attempts to do. The dotted curve is a forward accepted trajectory and replaces the solid curve to the right of shooting point 1. The dashed line is a subsequent backward accepted move from shooting point 2, and will replace the path to the left of shooting point 2 (both the solid and dashed parts). Thus, the path is now entirely different from the initial pathway and trajectory space is sampled more efficiently.

### 3. Transition path sampling for diffusive barriers

#### 3.1. One-way shooting

In the course of the path sampling we kept track of whether a trial trajectory shot was successful or not. When it still connected *A* with *B* it was denoted as an *AB* trajectory. The other possible outcomes were *AA*, *BB*, *BA*, short for trajectories that connected *A* with *A*, *B* with *B*, *B* with *A* (a reversed trajectory) respectively. Of course the trajectory can also fail to reach either stable state within a time  $\mathcal{T}$ ; this is denoted as *O*. All possible combinations and the frequencies of occurrence are summarized in table 1 for a TPS simulation for  $d = 11$ . In the standard path sampling algorithm, only the successful *AB* paths can be accepted. From table 1 it is clear that the acceptance is rather low, because many trajectories fail to connect *A* with *B* but connect *A* with *A* and *B* with *B* instead, or fail to reach any of these stable states and remain on the barrier. It would be very helpful if we could shoot a trajectory from a time slice in just one, arbitrary, direction, backward or forward in time and accept or reject if that new trial path is successful (see figure 2). For deterministic trajectories this is not possible because the sudden change of momenta somewhere along the path would interrupt the otherwise Newtonian *NVE* trajectory. The use of stochastic trajectories can eliminate this problem. In fact, in one of the seminal papers on TPS [2], it is shown that for stochastic (Brownian dynamics) trajectories the shooting move should be done in a single direction, either forward or backward in time. However, it is also useful to retain as deterministic a trajectory as possibly—for instance to be able to calculate microcanonical rate constants [6]. To introduce a little stochastic noise in an otherwise deterministic trajectory, we make use of the Andersen thermostat [8, 14]. The Andersen thermostat couples the system to a heat bath which reinitializes the momenta of a particle according to the Maxwell–Boltzmann distribution with a certain probability. If the frequency of this reassignment is sufficiently low, the dynamics of the trajectory should not

**Table 1.** Probabilities for trajectories to reach the stable states  $A$  or  $B$ , or stay on the barrier ( $O$ ) after a shooting move for a barrier length of  $d = 11\sigma$ . The shooting point was chosen on the barrier, with a maximum momentum displacement  $dp_{max} = 0.0001$ . The final acceptance probability for the shooting move was  $P_{acc} = 0.0557$ . The difference between this acceptance ratio and the  $AB$  trajectory number in the table is due to the fraction in equation (3).

Initial region	Final region		
	$A$	$B$	$O$
$A$	0.175	0.0735	0.1345
$B$	0.0375	0.177	0.0715
$O$	0.0735	0.1275	0.1275

be altered much, but because of molecular chaos, the trajectory will nevertheless soon diverge from the initial one. This means that one should only shoot from the neighbourhood of the barrier, just as is the case with stochastic trajectories [2, 7]. The Andersen thermostat was invented to perform constant-temperature  $NVT$  simulations by coupling to the heat bath, but one can choose to stay on the constant-energy ( $NVE$ ) surface by rescaling the kinetic energy of the particle back to the original value. If the total linear momentum has to be conserved as well, it is necessary to reinitialize two or more random particles at the same time. Detailed balance should be obeyed at all times, and if there are any constraints, the components of the momenta along these constraints should be removed [6]. For isolated systems the angular momentum can be kept constant as well [6].

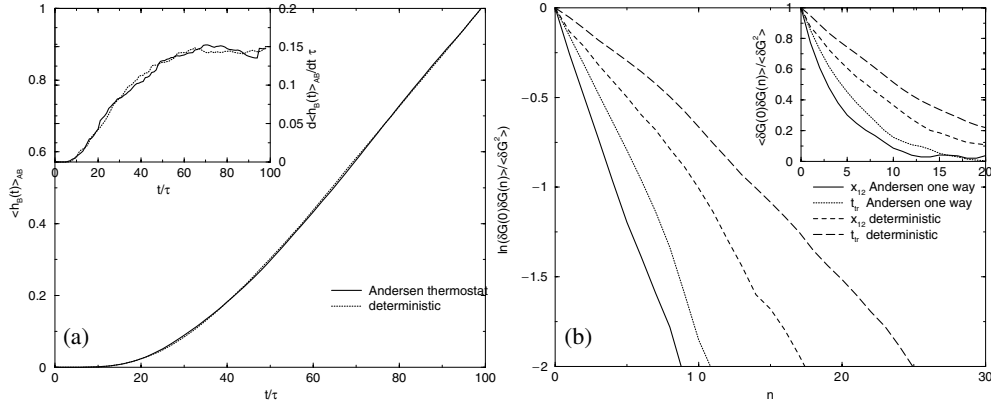
The new path sampling algorithm now becomes as follows: start with an initial path of  $L$  time slices connecting  $A$  and  $B$  (for more details on how to create an initial path see [6]). Let  $t_A^{(o)}$  be the time just before leaving  $A$  and  $t_B^{(o)}$  the first time the system enters  $B$  on the old path. Now choose a slice  $t'$  on the barrier between  $t_A^{(o)}$  and  $t_B^{(o)}$  with a uniform probability (or with a biasing function). Next, integrate the equations of motion forward to  $t = \mathcal{T}$  and backward until time  $t = 0$  using the Andersen thermostat as a stochastic noise generator. If the new trial path still connects  $A$  with  $B$ , the shot is accepted with a probability according to equation (3). If the backward path reaches  $A$  but the forward shot fails to end in  $B$ , the forward trajectory is rejected and the old forward part is retained. The old backward path from  $t = t'$  to 0, however, is replaced by the new backward trajectory, and accepted with the probability in equation (3). Similarly, if the forward path reaches  $B$  but the backward shot fails to end in  $A$ , the forward trajectory is substituted from  $t = t'$  to  $\mathcal{T}$  and accepted with the same acceptance probability (3). Shifting moves are performed as usual [6].

### 3.2. Numerical results

We tested the new algorithm on the two-state system described in section 2.2 with a large distance  $d = 11$  to make the system diffusive enough. The acceptance for the original shooting move is rather low,  $P_{acc} \approx 0.056$ . In contrast, the acceptance of the forward and backward Andersen one-way shooting move is much higher,  $P_{acc} \approx 0.55$ , thus considerably improving the sampling.

The question arises, however, of whether the Andersen thermostat trajectories are a good approximation for the deterministic ones. If the frequency of reassigning velocities is low enough, the dynamical properties such as the diffusion constant should not be affected too much; see e.g. [14]. In fact, our frequency is rather low, as a two-particle reassignment is done once every thousand time steps. This corresponds to an update frequency of  $\nu = 0.00066$ . For comparison we plotted in figure 3(a) the correlation function  $\langle h_B(t) \rangle_{AB}$  and its derivative





**Figure 3.** (a) Comparison between the new one-way Andersen shooting scheme and the original deterministic algorithm for the correlation function  $\langle h_B(t) \rangle_{AB}$  and its derivative  $\langle \dot{h}_B(t) \rangle_{AB}$  (inset). (b) The logarithm of the autocorrelation function  $c(n)$  as a function of the number of simulation cycles, for sampling with and without the Andersen thermostat. The barrier width  $d = 11\sigma$ . Two different quantities  $G$  were used: the transition time  $t_{tr}$  and the particle distance  $x_{12}$  halfway across the barrier.

$\langle \dot{h}_B(t) \rangle_{AB}$  with and without the Andersen thermostat, where the brackets with subscript  $AB$  denote an average performed in the path ensemble. The agreement is excellent and we expect the dynamical properties such as the rate constant to be adequately close to the microcanonical values [14].

One might object that while the new Andersen one-way algorithm has improved the acceptance probability, the efficiency might not be better because the barrier is only sampled rarely. This leads to strong correlation between consecutive paths and hence to poor efficiency. Therefore, we computed the efficiency as in [4] from the autocorrelation function  $c(n)$  of the fluctuation of a quantity  $G$  as a function the number  $n$  of simulation cycles:

$$c(n) = \frac{\langle \delta G(0) \delta G(n) \rangle_{AB}}{\langle \delta G^2 \rangle_{AB}}, \quad (4)$$

where  $\delta G(n) \equiv G(n) - \langle G \rangle_{AB}$ . One can choose many functions for  $G(n)$ , and here we choose the transition time  $t_{tr} = t_B - t_A$ , the time that the system spends on the barrier, and the distance between the two double-well particles  $x_{12}((t_A + t_B)/2)$  halfway across the barrier. A high efficiency is indicated by a fast decay of the autocorrelation function and in figure 3(b)  $c(n)$  does indeed decay quickly to zero. As in [4] we can estimate the number  $n_c$  of correlated cycles by defining a threshold below which the paths are assumed to be uncorrelated, or alternatively by integrating the autocorrelation function. Integrating the function  $c(n)$  leads to an estimate of  $n_c \approx 5$  for the Andersen scheme and  $n_c \approx 15$  for the original TPS algorithm. Interestingly, the two chosen functions  $G(n)$  give similar estimates for  $n_c$ .

This analysis suggests that the new scheme is more efficient by a factor of 3 for this particular system. For more complex processes we expect the TPS with the ordinary shooting move to break down completely. Indeed, preliminary calculations show that for biomolecular isomerization there is no acceptance at all when using the original shooting move [15]. In that case, the Andersen one-way shooting method advocated here might enable proper sampling of the path ensemble.



#### 4. Conclusions

We have introduced an adapted stochastic TPS algorithm to sample diffusive barriers, based on the Andersen thermostat. The new sampling scheme has all the advantages of the original TPS method, including the microscopic dynamical information, and the freedom from imposing reaction coordinates, but increases the acceptance probability and hence the sampling efficiency dramatically. Further improvement of efficiency can be achieved by allowing the path length to fluctuate, in order to reduce the number of required MD time steps. We will report on this in a future publication [15].

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